

Appl. No.: 10/674,750  
Filed: September 30, 2003  
Page 12

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### **REMARKS/ARGUMENTS**

#### **Status of the Claims**

Claims 1-14 have been canceled without prejudice to or disclaimer of the subject matter encompassed thereby. Claims 21-31 have been added.

Support for the new claims resides in the specification and the claims as originally filed. Specifically, claims 21-29 find support in the originally filed claims and in the specification on page 11, line 12, continuing through to page 12, line 31. Claims 30 and 31 find support in the specification in Tables 1 and 2 found on pages 7-9. No new matter has been added by way of presentation of new claims.

Claims 15-31 are now pending in the application. Reexamination and reconsideration of the claims are respectfully requested in view of the following remarks. The Examiner's comments in the outstanding Office Action are addressed below in the order set forth herein.

#### **The Objections to the Specification Should Be Withdrawn**

Responsive to the Examiner's objections regarding the use of trademarks, the specification has been amended to identify the recited trademarks. Specifically, trademark designations have been capitalized, or the <sup>TM</sup> symbol has been removed if it does not identify goods in trade. As the marks are used in context and the identity of the product is fixed and unambiguous, the specification is now compliant. According to the M.P.E.P. §608.01(v), a trademarked term is acceptable where it is unambiguous. Accordingly, Applicants respectfully submit that the proprietary nature of the marks has been respected, and the objections to the specification should be withdrawn.

In addition, the specification has been amended to correct inadvertent misspellings of the term "tetrazolium" recited in the paragraphs beginning on page 26, line 23 and beginning on page 27, line 6; the terms "neurodegenerative" and "Huntington's" in Table 1, page 8; and the term "than" in the paragraph beginning on page 32, line 22.

RTA01/2(60570v)

Appl. No.: 10/674,750  
Filed: September 30, 2003  
Page 13

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It is noted that the Office Action Summary Sheet indicates that claim 20 is objected to. However, there is no subsequent description in the Office Action of the basis for the objection. Applicants respectfully request clarification regarding the objection.

The Rejections of the Claims Under 35 U.S.C. §112, First and Second Paragraph, Should Be Withdrawn

Claims 1-3 and 5-13 are rejected under 35 U.S.C. §112, first paragraph, for lack of an enabling specification. Applicants respectfully submit that original claims 1-3 and 5-13 were enabled by the specification for the reasons noted below. However, to further prosecution, the claims have been cancelled and subject matter encompassed by these claims is now set forth in newly presented claims 21-31. To the extent that the new claims find support in the canceled claims, the rejection is respectfully traversed.

As an initial matter, Applicants respectfully note that limitation of the claims to the working examples is improper, especially where the claims are afforded the presumption of enablement, and the U.S.P.T.O. does not assert evidence rebutting this presumption. See M.P.E.P. §2164.02. It is noted that no factual evidence was submitted by the U.S.P.T.O. that demonstrated that the claimed invention would not work as described. The number of publications on ion-induced protein aggregates was mentioned, but these publications are not germane to methods of making the metal-cluster nucleated compositions of the invention. The methods as described in the specification generally require that one heat and apply pressure to a sample. Thus, the art is very predictable. Alternatively, if the Office Action is asserting that such methods of applying heat and pressure are unlikely to create proteons, then the objective truth of the claimed methods is being questioned, and the U.S.P.T.O. will be required to explain why the truth or accuracy of such claims should be doubted. M.P.E.P. §2164.04.

It is also noted that a lack of prior published work in an art neither supports nor rejects the notion of underlying predictability of the art itself. It simply demonstrates the novelty and non-obviousness of Applicants' invention. In fact, the lack of publications demonstrates that there is no evidence that could be asserted to rebut the presumption of enablement. Therefore,

RTA01/2160570v1

Appl. No.: 10/674,750  
Filed: September 30, 2003  
Page 14

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unless the Examiner has special individual knowledge regarding unpredictability in the art and submits an affidavit to that effect under 37 C.F.R. §1.104(d)(2), Applicants' burden is met and remains un rebutted.

Finally, Applicants note that at least nine working examples are disclosed (see Examples 1-9) that demonstrate methods of manufacture as well as biological effects of proteons and PNCs. Thus, even if the U.S.P.T.O. could rebut the presumption of enablement, disclosing such a large amount of data in multiple working examples satisfies the burden. For these and the reasons discussed *supra*, the rejection should not be asserted against the new claims.

Claims 1-3, 4, and 5-13 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Applicants respectfully submit that the original claim language was definite as submitted. However, to further prosecution, these claims have been canceled, and subject matter encompassed by these claims is now set forth in newly presented claims 21-31. To the extent that the new claims find support in the canceled claims, the rejection is respectfully traversed.

Specifically, the heating times and cycles recited in the claims have been reworded to further clarify the claimed subject matter. Thus, independent claims 21 and 30 recite that the subsample is heated and the method steps are repeated for 1 or more cycles. Dependent claims 24 and 26 further delimit the heating times and number of cycles, respectively. That subject matter encompassed by canceled claim 4 is now set forth in new claim 30. Claim 30 provides proper antecedent basis for the phrase "the proteons produced" and further recites the proteins listed in Tables 1 and 2. Dependent claim 31 recites the disorders listed in Tables 1 and 2. For these reasons, claims 21-31 are also definite, and thus the rejection should not be asserted against the new claims.

The Rejections of the Claims Under 35 U.S.C. §102(b) Should Be Withdrawn

Claims 15-18 are rejected under 35 U.S.C. §102(b), in light of Bush *et al.* (1994) *Science* 265:1464-1467 (cited in the IDS filed February 17, 2004). This rejection is respectfully traversed.

RTA01/2160570v1

Appl. No.: 10/674,750  
Filed: September 30, 2003  
Page 15

Bush *et al.* do not disclose metal clusters of any kind, such as zinc metal clusters. Metal clusters are known in the art to be aggregates of two or more atoms that are bonded to each other by sharing valence electrons. See, for example, *McGraw-Hill Dictionary of Scientific and Technical Terms* (1994, New York), and Iapov *et al.* (1998) *J. Phys. B: At. Mol. Opt. Phys.* 3:L27-34. Bush *et al.* disclose protein aggregation mediated by zinc cations ( $Zn^{2+}$ ) binding the amino acid histidine, which has an ionizable side chain. Bush *et al.* at 1465.

Bush *et al.* cannot anticipate because the cations are in the form of soluble metal salts (e.g.,  $Zn^{2+}$  and  $Cl^-$ ) not metal clusters (i.e., bonded metal atoms). In fact, in all of the experiments of Bush *et al.*, metal salts (i.e., ions) are used. *Id.* at Figure 2, p. 1465. Further, Bush *et al.* teach recovery of ionically aggregated protein from a retentate after ultrafiltration. In contrast, Applicants teach recovery of proteon nucleation centers (PNCs) comprising a metal cluster from a filtrate. Thus, because the cited reference does not teach metal clusters or methods of purification thereof, this rejection of the claims should be withdrawn.

Claims 15 and 19 are rejected under 35 U.S.C. §102(b), in light of Campbell *et al.* (2001) *Brain Res. Bull.* 55:125-132 (cited in the IDS filed February 17, 2004). This rejection is respectfully traversed.

Campbell *et al.* describes an aggregation of prion proteins using solvated metal ions. As discussed *supra*, metal ions used in this manner do not form metal clusters (i.e., metal atoms which bind to each other). Moreover, the biological effects taught by Campbell *et al.* are limited to such protein aggregates. Therefore, as Campbell *et al.* does not teach metal clusters, or protein aggregates comprising such clusters, or the biological effects of the foregoing, it cannot anticipate. Accordingly, this rejection of the claims should be withdrawn.

### CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the objections to the specification and rejections of the claims under 35 U.S.C. §112, first and second paragraphs, and §102(b) are now overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited. If, in the

RJA01/2160570v1

Appl. No.: 10/674,750  
Filed: September 30, 2003  
Page 16

opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR §1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

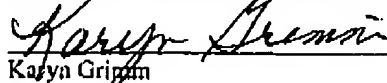


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CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the US Patent and Trademark Office at Fax No. (703) 872-9306 on the date shown below.

  
Karyn Grimm

January 4, 2005  
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RTA01/2160570v1